Aldosterone

Introduction

This lesson is about the details of aldosterone and the disease states associated with having too much or too little of it. The thing is, we've talked about aldosterone so much in other organ systems that there isn't much new here. We bring up a new discussion about an old theme—water vs. salt—then discuss aldosterone in the context of how you learned it from the perspective of the adrenal gland—as a steroid hormone. We then review the renin-angiotensin-aldosterone system and its regulation and cover the work-up and management of secondary hypertension caused by aldosterone excess.

Water vs. Salt

Learners quickly become confused when dealing with water and sodium. If you get the next few lines intuitively, you can skip the remaining paragraphs. If you don't already have mastery over these statements but understand them, read the next few paragraphs anyway. **Aldosterone triggers the reabsorption of sodium**, and because water follows salt, the **reabsorption of sodium leads to an increased circulating volume and no change in serum sodium.** In contrast, **antidiuretic hormone triggers the reabsorption of water**, and because serum sodium is a marker for tonicity, the **reabsorption of water dilutes the plasma,** so **sodium decreases**.

The concepts of **free water** and **volume** are related but not the same. Free water does have a volume—you can drink a gallon of tap water or infuse 500 cc of D5W. But **free water** should be seen only as a diluting step, which changes the plasma concentration. This becomes intuitive in clinical medicine but is frustrating in the basic sciences. When you believe someone is volume depleted, as in a septic patient, the standard protocol is to bolus 30 cc/kg of lactated ringers or normal saline. That's usually 2 L or more of **isotonic volume**. You do that to correct their volume, their blood pressure, their hemodynamics. If their heart rate comes down, their blood pressure comes up, and markers of impaired tissue perfusion decline, you then say, "they've been repleted." If they don't, you consider more volume or vasopressors. If you give a 2-L bolus of D5W, which is essentially pure water, you will immediately kill the patient. That amount of dilution that fast cannot be tolerated by cells. By tanking the plasma concentration (called osmolarity), you tank the concentration of the extracellular space surrounding cells. Remember Gen Chem? "*When there is a lot of water on one side of a semipermeable membrane and not on the other, water shifts away from the side with the most water to the more concentrated side.*" Now, it's plasma membranes. Low concentration outside the cell, higher concentration within the cell, water moves into the cell. The cells swell, lyse, and die. It wasn't that the blood vessels couldn't tolerate the 2 L of volume, it's that the fluid shifts of cells everywhere (especially neurons and the cells of their myelin sheath) couldn't tolerate the change in osmolarity (the concentration of the extracellular fluid).

The calamity comes mostly in the collecting duct. The tubules automatically reabsorb almost all of the filtered water and sodium (97% of each). No regulation, no hormonal influence. What doesn't get reabsorbed is delivered to the collecting duct. Under the influence of **ADH, aquaporin channels** are inserted in the luminal membrane. This makes the normally impermeable-to-water membrane permeable, and water is reabsorbed. If all that happened were ADH activity, and **only water were reabsorbed**, the serum **osmolarity would go down**. Under the influence of **aldosterone**, **ENaC channels** are inserted into the luminal membrane. This changes the permeability of the membrane for Na^+ from impermeable to permeable. If all that happened were aldosterone activity, and **only sodium were reabsorbed**, the **osmolarity would not change**, but the **volume would increase**. Because an osmotically active compound is in the blood, fluid from anywhere else would balance its osmotic force, and volume would stay in the blood vessels. If there were equal ADH and aldosterone activity, and both sodium and water were reabsorbed, the volume OBVIOUSLY would go up without a concentration change because the water and the sodium would be leaving together.

Here's the final element of difficulty. Aldosterone leads to the reabsorption of sodium. ADH leads to the reabsorption of water. Sodium is a marker of tonicity, not of sodium levels. The serum sodium on the basic metabolic profile changes with ADH activity and does not change with aldosterone activity.

The macula densa cares about circulating volume, perfusion pressure, and GFR. It senses flow. It activates the renin-angiotensin-aldosterone axis so that aldosterone can reabsorb sodium. Angiotensin-2 (Ang-2) also stimulates ADH secretion by the hypothalamus, regardless of what it is sensing in the way of osmolarity or circulating volume. Ang-2 hijacks ADH because it knows that with aldosterone and ADH, there will be reabsorption of volume without alteration of the osmolarity.

Effects of Aldosterone

We've seen these effects discussed in Renal and Cardiac, but they are worth repeating here as it is a follow-up to the previous section, written differently to impart the same wisdom with a different strategy.

Wherever ENaC channels are inserted, aldosterone is the mechanism by which they are regulated. Aldosterone is a mineralocorticoid, and it binds to **mineralocorticoid receptors**. Because it is a steroid hormone, like cortisol, it freely diffuses across plasma membranes. Mineralocorticoid receptors are **cytoplasmic receptors** that are stabilized by their chaperone, Hsp90. The binding of the mineralocorticoid to its receptor induces its release from the chaperone and translocation to the nucleus, where the hormone-receptor complex binds to DNA and modulates gene transcription. In all cells that make ENaCs—sweat glands, salivary glands, and, most importantly, the collecting duct of the renal tubules—aldosterone will **increase the gene transcription of ENaC**. The more ENaCs there are, the more sodium will be reabsorbed from whatever duct it is inserted into. In the collecting duct, ENaC channel gene transcription determines how much of that remaining sodium (3% of what was filtered) will be reabsorbed.

Aldosterone determines extracellular volume by controlling the extracellular Na^+ levels. Na^+ in the extracellular space retains water—it is the primary osmotically active particle in the extracellular space—and thus, the amount of Na^+ present determines the volume of extracellular fluid. The extracellular volume is itself a prime determinant of arterial blood pressure, and therefore aldosterone plays an important role in the maintenance of blood pressure. Aldosterone determines **Na^+ levels** and, therefore, volume. The thing you get on a BMP is a concentration, not total body sodium.

The effects of aldosterone on salt balance determine the extracellular volume and should not be confused with the effects of ADH. ADH regulates the free-water balance of the body. Water freely passes across most cell membranes, affecting the concentration of Na^+ and other solutes throughout the body. Unlike aldosterone, ADH makes only a small contribution to the maintenance of extracellular volume; instead, ADH regulates serum osmolarity and, therefore, the Na^+ concentration. ADH determines **Na^+ concentration**, and thus the thing on the BMP is a reflection of free water, which in turn is a reflection of ADH.

Thus, to a first approximation, one can think of aldosterone as the primary regulator of extracellular volume because of its effect on renal Na^+ reabsorption, and ADH as the primary regulator of plasma osmolarity because of its effect on free-water balance.

Another important role of aldosterone is the **regulation of K^+**. The ENaC channels require an electroneutral exchange for the reabsorption of Na^+. In the renal collecting duct, the ion that does that is K^+. With aldosterone excess, potassium levels can get quite low. A low K^+ is most likely to provoke **weakness** or **temporary paralysis**. Conversely, a deficiency in aldosterone leads to a precipitous rise in serum potassium levels. High K^+ is most likely to induce cardiac arrhythmia. Under normal conditions, the potassium swings induced by dietary irregularity are stabilized by aldosterone.

Finally, aldosterone affects the **intercalated cells** of the collecting duct as well. Aldosterone's presence increases the transcription of the luminal **H^+-ATPase**. Carbonic anhydrase generates an H^+ and an HCO_3^-. The H^+ is released into the tubule lumen, and the HCO_3^- is released into the bloodstream. This results in the acidification of the urine and the alkalization of the blood. This is the primary mechanism by which the kidney accounts for acidosis.

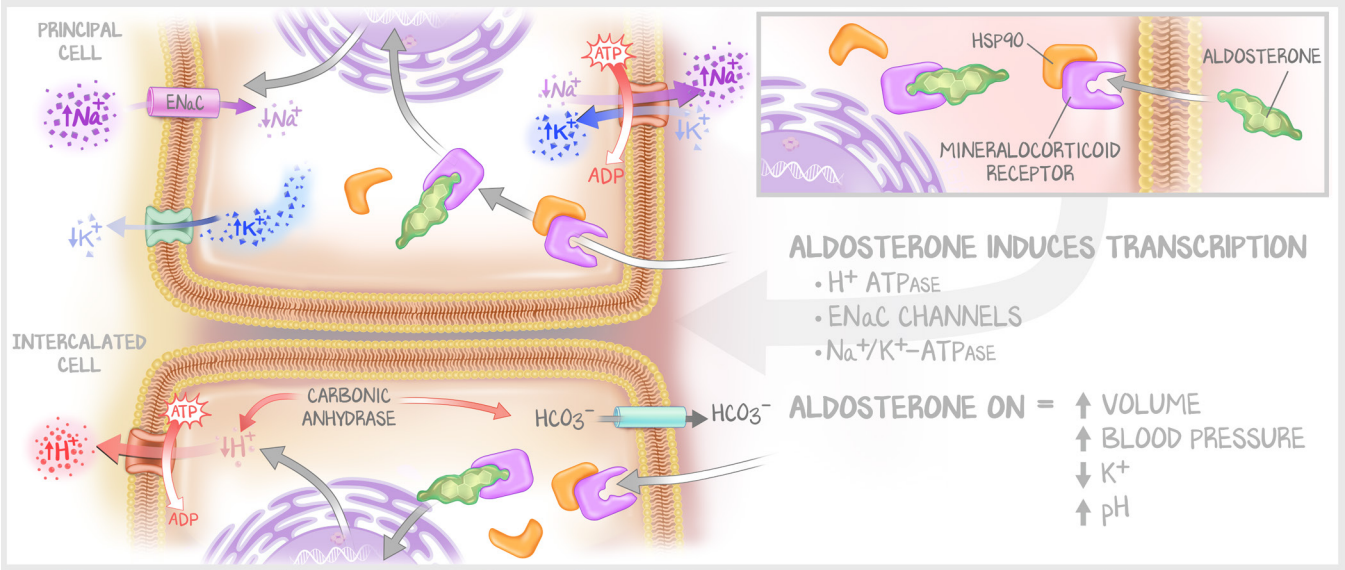

Figure 3.1: Aldosterone's Actions
Aldosterone is a steroid hormone that binds to cytoplasmic receptors, displaces the chaperone Hsp90, and translocates with its receptor into the nucleus. There, it induces transcription of basolateral Na^+/K^+-ATPases, ENaC channels in chief cells of the collecting duct as well as ductal cells of sweat glands and salivary glands, and H^+-ATPase in the intercalated cells of the collecting duct. The net effect is an increase in blood volume (preload, blood pressure), wasting of potassium, and alkalization of the blood.

Regulation of Aldosterone Expression: Renin

In the Renal module, we introduced the "Katrina switch" model for comprehending the macula densa and the JG apparatus (Renal: Kidney #3: *Glomerular Filtration*). Figure 3.6 from that lesson is reproduced here. The key to the comprehension of this system is understanding that the macula densa acts as a **flow sensor**, using the flow through the tubules as an estimate for the flow across the glomerular capillary—**glomerular filtration rate**. The Katrina switch is named after hurricane Katrina, which struck New Orleans in 2005. When Dr. Williams bought his house there after medical school, some light switches were installed upside down. The upside-down light switch is crucial to understand the system. If the GFR is high, there is lots of flow through the tubule, and the switch is pushed up by the force of flow to the "off" position. If the GFR is low, there is not a lot of flow through the tubule, and the switch falls to "on" due to gravity.

When the switch is on, the macula densa informs the JG cells of the JG apparatus to release renin. **Renin** is the primary endocrine driver of aldosterone synthesis. Renin is released into the bloodstream where it converts **angiotensinogen**, a precursor molecule made by the liver, to angiotensin-1. In the lungs, angiotensin-1 is converted to **angiotensin-2** by **angiotensin-converting enzyme** (ACE). Angiotensin-2 (Ang-2) then has several downstream effects. It induces vasoconstriction in all arterioles of all capillary beds (angiotensin-2 "tenses the angios"). The intended effect is to constrict the efferent arteriole while local tubuloglomerular feedback prevents the constriction of the afferent arteriole. This provides an increased hydrostatic force to increase the GFR. The kidney uses flow through the glomerulus as a surrogate for GFR and GFR as a surrogate for the patient's overall volume status.

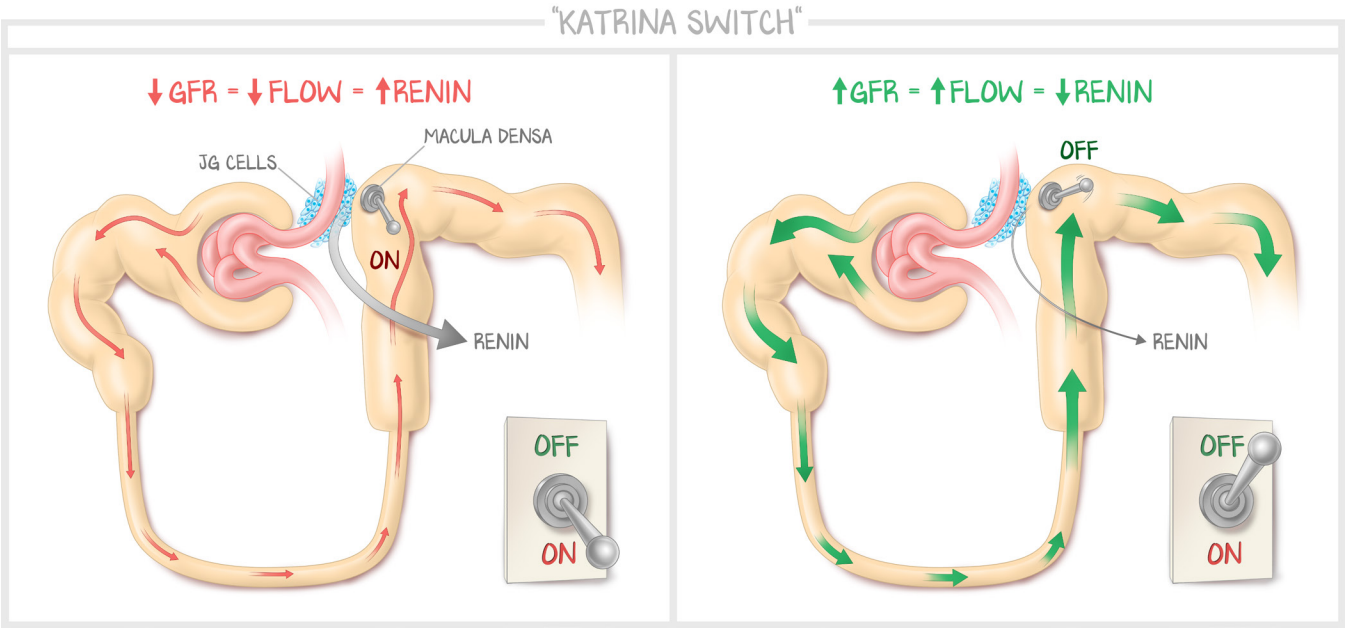

Figure 3.2: The Katrina Switch
A visualization of the Katrina switch as a teaching tool for how the macula densa acts as a flow sensor and how it acts as an effector of systemic hypertension. We've chosen to depict only the release of renin in relation to the switch being on or off so as not to convolute the illustration. We started the discussion in Renal (this illustration should be familiar) and now continue it here in Endocrine. When the switch is on, renin is on, and the RAAS is active.

The switch is on when GFR is low. The JG apparatus assumes the cause of a low GFR is poor perfusion pressure and acts to both fix the flow into the capillary from which the JG apparatus assesses flow AND send hormone signals in an attempt to correct the overall volume status of the patient. We gave a glancing blow to this system in Cardiac: Hemodynamics #4: *Blood Pressure Regulation*. Angiotensin-2 "tenses the angios," causing systemic vasoconstriction, and aldosterone induces the reabsorption of sodium (volume). But angiotensin-2 does more than just "tense the angios"; it is the signal for the release of both ADH from the posterior pituitary and aldosterone from the adrenal cortex. **Angiotensin-2 directly stimulates the zona glomerulosa to increase aldosterone synthesis**. Ang-2 binds the **angiotensin-2 type 1 (AT1) receptor**, which is a G protein-coupled receptor. Stimulation of AT1 receptors by Ang-2 results in the activation of the G_q-IP_3-Ca^{2+} pathway. The exact mechanism of how calcium increase results in increased aldosterone synthesis is not well elucidated. However, it *is* known that no storage pool of presynthesized aldosterone is available in the glomerulosa cells for rapid secretion (just like with cortisol, which is also a lipid-soluble steroid hormone). Therefore, the rate of secretion is the same as the rate of synthesis—transcription and translation. The increased production likely comes either from the rate of synthesis of aldosterone synthase (the final step in aldosterone synthesis) or simply the rate of synthesis of the enzyme that is the rate-limiting step of all steroid hormone synthesis—the first one, and the one we have suggested you do not learn. The point is, more Ang-2, more AT1-receptor activation, more aldosterone synthesis.

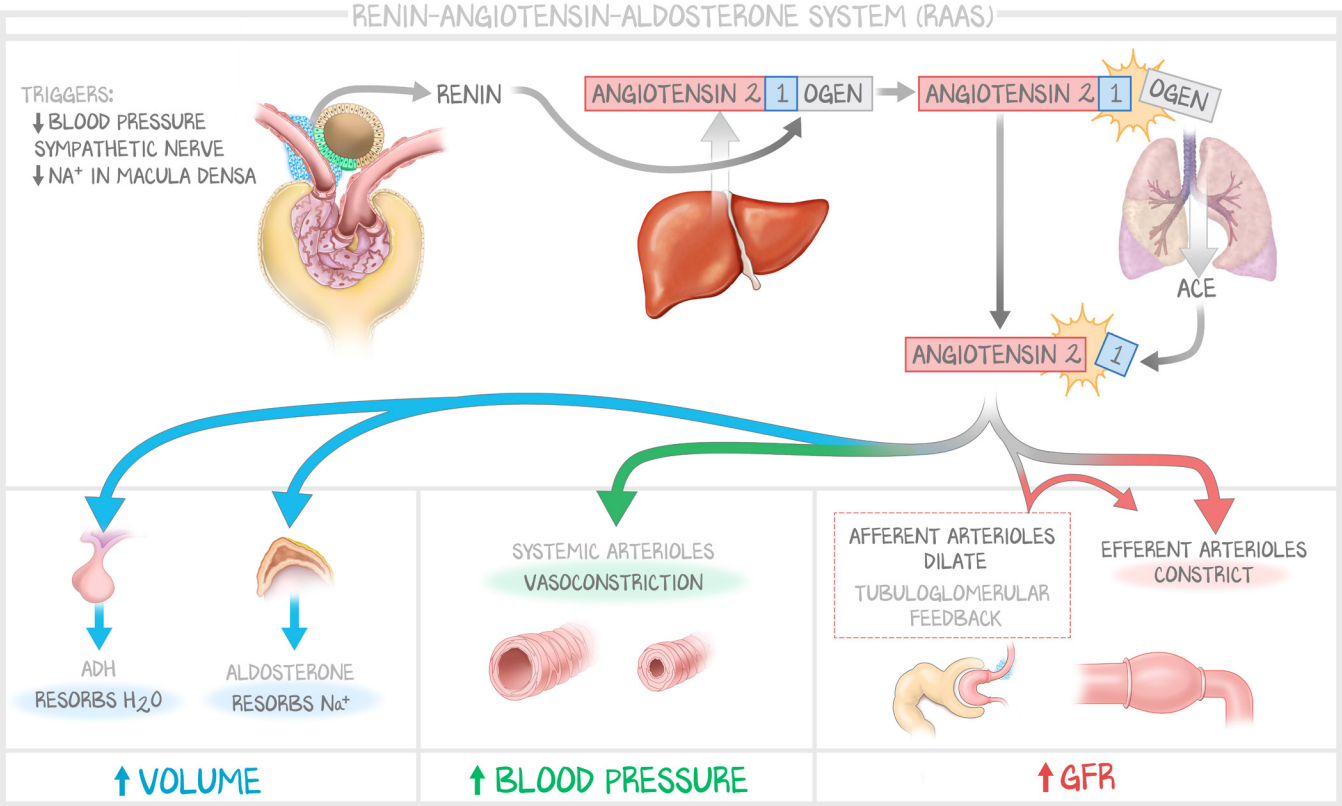

Figure 3.3: Full Extent of the Renin-Angiotensin-Aldosterone System
Activation of the JG apparatus leads to the release of renin, conversion of angiotensinogen to angiotensin-1, and conversion of angiotensin-1 to angiotensin-2. Angiotensin-2 leads to the vasoconstriction of systemic arterioles, increasing systemic vascular resistance, and thereby increasing blood pressure. Angiotensin-2 likewise vasoconstricts the arterioles of the glomerulus. The afferent arteriole is informed by the JG apparatus, through tubuloglomerular feedback, to remain dilated while the efferent arteriole vasoconstricts. This ensures greater hydrostatic force between them, leading to a greater GFR, but has no impact systemically. Ang-2 induces the release of ADH from the posterior pituitary and increases aldosterone expression from the adrenal gland. Aldosterone then acts on the principal cells to reabsorb sodium (volume). ADH acts on principal cells to reabsorb water. The RAAS, therefore, increases blood pressure via angiotensin-2 (SVR, "tenses the angios") and increases circulating volume (preload, ADH, and aldosterone).

Extracellular potassium, another mechanism of aldosterone release. Cells of the zona glomerulosa are excitable cells. They have a Na^+/K^+-ATPase and K^+ leak channels. The leak channels have poor conductance, and that conductance changes based on the extracellular potassium (General Physiology #6: *Excitable Cells: Passive Properties*, Figure 6.5). High extracellular potassium worsens the concentration gradient and reduces the efflux of potassium. This moves the resting membrane potential away from the Nernst potential for K^+, depolarizing the cell. That depolarization is just like the effects of ACTH-G_q-IP_3-Ca^{2+}. Because increased K^+ and Ang-2 both act by raising intracellular Ca^{2+}, they can act synergistically on glomerulosa cells. **Hyperkalemia leads to depolarization** of the cell, resulting in the **same outcome as AT1** receptor stimulation.

Signs and Symptoms, Work-up of Aldosterone Excess

The main effect of aldosterone is in the collecting ducts. The increased activity of the mineralocorticoid receptor upregulates ENaC expression and carbonic anhydrase expression. ENaCs cause the reabsorption of Na^+ and the simultaneous wasting of K^+. The sodium reabsorption leads to volume expansion. Thus, **hypertension and hypokalemia** is the classic paired finding (though now we know that most cases of hyperaldosteronism do not present with hypokalemia). For your licensing exam, in order to detect when a vignette is telegraphing hyperaldosteronism, look for refractory hypertension WITH hypokalemia. When you see a patient with secondary hypertension in clinical practice, the following work-up will be part of the initial screening.

The diagnosis of primary aldosteronism starts with a plasma **aldosterone-renin ratio** (ARR). By measuring the relative levels of aldosterone and renin, it can be determined whether excess aldosterone is present, and by which mechanism—because renin is increased, driving aldosterone to rise, or because aldosterone is being autonomously secreted without a renin signal. If there is an **elevated ARR** (> 30), it is primary hyperaldosteronism. If there is a **normal ARR** (< 10), the diagnosis is secondary hyperaldosteronism, called **renovascular hypertension.**

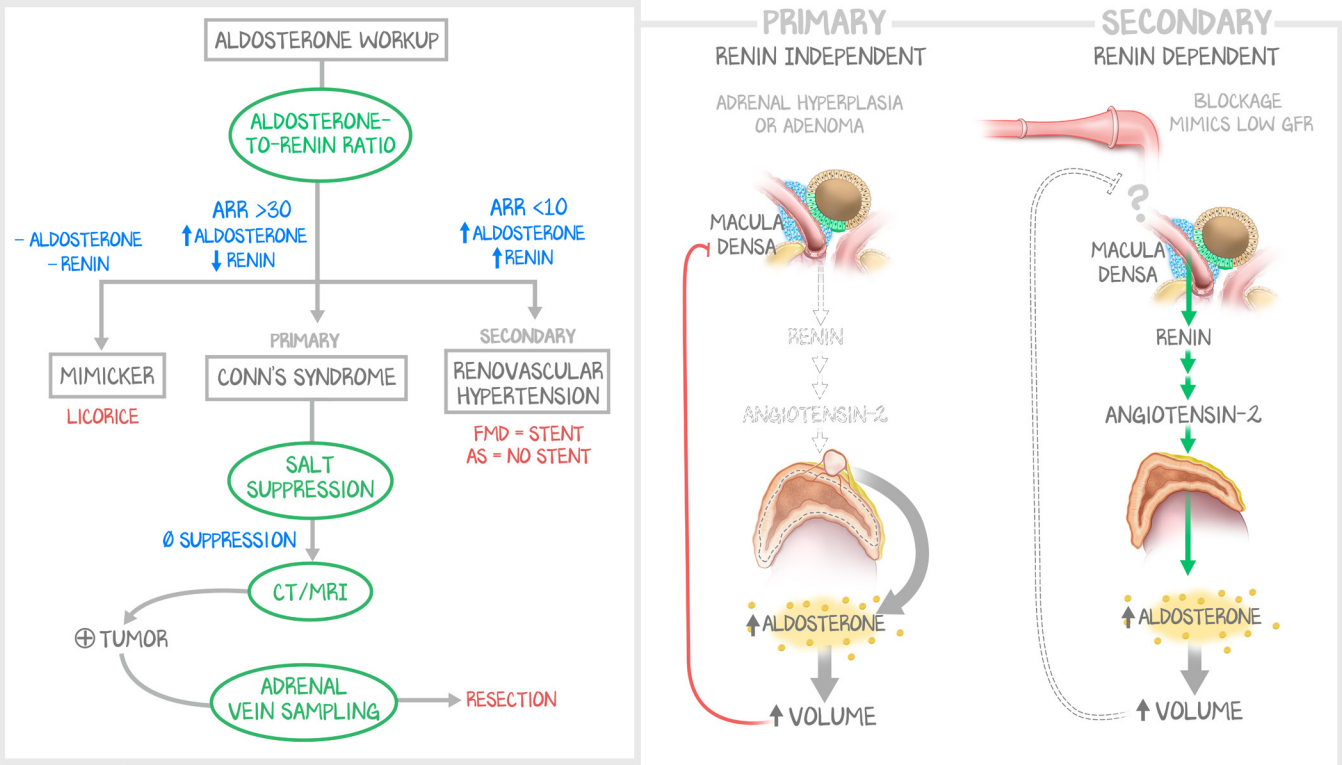

Figure 3.4: Aldosterone Work-up
When hyperaldosteronism is expected, the work-up begins with an aldosterone level, renin level, and aldosterone-to-renin ratio (ARR). If the ARR < 10 but aldosterone is elevated, it is likely to be renovascular hypertension. If the ARR > 30, primary hyperaldosteronism is likely. If aldosterone is not elevated, it may be a mimicker. In the path to diagnosing primary aldosteronism, there are interceding diagnostics. Salt suppression is done to ensure that the cost of a CT or MRI is worth doing. The CT or MRI is done to ensure that surgical exploration for adrenal vein sampling is worth the risk. Ultimately, adrenal vein sampling must be performed to ensure the laterality of a hyperfunctioning gland. Primary hyperaldosteronism is caused by an adrenal adenoma. Secondary hyperaldosteronism is caused by the failure of the macula densa to sense a normal GFR.

Primary Hyperaldosteronism

Primary hyperaldosteronism stems from the autonomous overproduction of aldosterone **by the adrenal gland** without a RAAS signal. In this case, the downstream effector, **aldosterone, is elevated,** but the first signal to initiate the endocrine pathway, **renin, is low**. Primary aldosteronism is caused either by hyperplasia of both adrenal glands or a unilateral aldosterone-producing adenoma

An **aldosterone-producing adenoma** is known as Conn's syndrome. This syndrome occurs most frequently in middle-aged adults and is more common in women than in men (2:1). To find the tumor, the best first step in imaging is **a dedicated adrenal CT** (or MRI). In one-third of patients, the CT may not identify the cause of primary aldosteronism because some are too small to see, or there is an incidental adrenal mass unrelated to primary aldosteronism. Consequently, most patients with confirmed primary aldosteronism **should undergo adrenal vein sampling** to confirm the source of the hyperaldosteronism. This is very different from hypercortisolism, where adrenal vein sampling is not indicated. Resection of the adrenal gland restores normal functioning. **Laparoscopic adrenalectomy** is effective for unilateral disease and reduces plasma aldosterone and its attendant increased risk of cardiovascular disease.

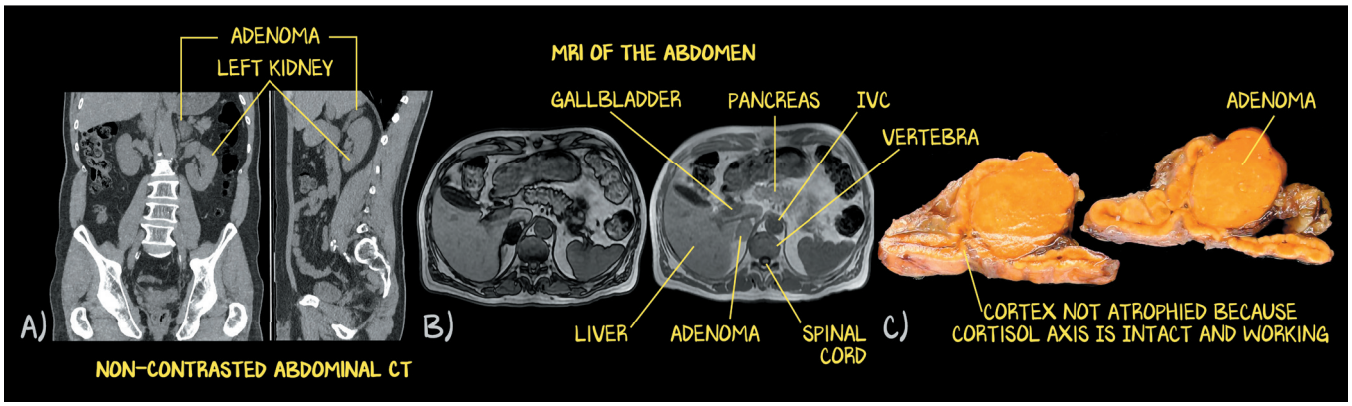

Figure 3.5: Primary Hyperaldosteronism
(a) Two views from a non-contrast abdominal CT reveal an adrenal adenoma. Check out the supplementary video, where Dr. Williams actually spins through the film. It's usually more difficult to make out, but we've doctored this photo to make it visible to you by combining three slices. (b) Axial section from the same patient is shown in two modes. They are both T1-weighted (the liver is grey, the air in the bowel has texture). The right image is labeled to show you where to look in the left image, which is in a mode that best detects adrenal adenomas (it stands out the best), but we're not naming it because you definitely do not have to know MRI modes. We are immersing you in T1 vs. T2, but not beyond that. (c) Two slices of the same adrenal gland reveal a cortical mass. The size of this adenoma is unusual for hyperaldosteronism (they are usually smaller), but we chose a sample that was easy to see. Most importantly, notice the absence of atrophy of the cortex. Histologically, the zona glomerulosa will be thinner, but the fasciculata and reticularis will function normally.

Bilateral idiopathic hyperaldosteronism (IHA), characterized by bilateral nodular hyperplasia of the adrenal glands, is the most common underlying cause of primary hyperaldosteronism, accounting for about 60% of cases. Individuals with idiopathic hyperaldosteronism tend to be older and have less severe hypertension than those with APA. These patients benefit from specific medical therapy with **aldosterone antagonists** and not surgery. IHA isn't an out-of-control adenoma, and it isn't a confused macula densa. IHA is likely a symptom of something else, not the primary problem. IHA drives hypertension, and so the hypertension is treated. It isn't an endocrine problem with an endocrine solution, but a hypertension problem with a hypertension solution.

Secondary Hyperaldosteronism

Secondary hyperaldosteronism is characterized by **increased levels of plasma renin**. This is the appropriate response to volume contraction and a falling GFR—renin goes up, so Ang-2 goes up, so

aldosterone goes up to restore volume. There are, however, certain times when the macula densa senses decreased flow, but the body is not in a volume-contracted state, and there is inappropriate activation of the RAAS. To be clear, the macula densa is working appropriately, and there is no tumor of the macula densa that secretes renin—it's just that the following conditions trick the macula densa by causing a reduced GFR without causing a loss of circulating volume.

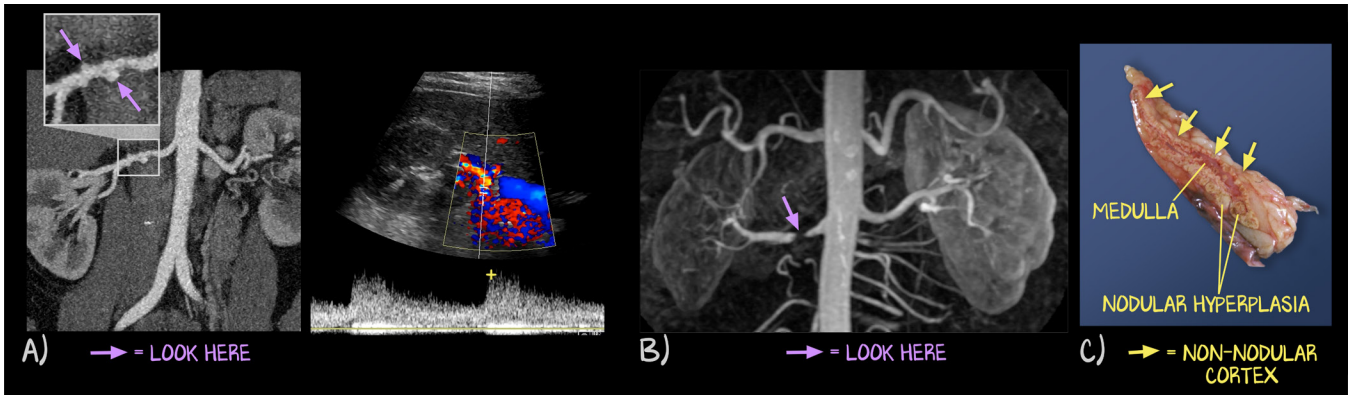

Figure 3.6: Renovascular Hypertension
(a) Angiogram (MRI angiogram, MRA) demonstrating the beaded appearance of the right renal artery (left side of image), diagnostic of fibromuscular dysplasia. The image on the right is an ultrasound with duplex, a vascular ultrasound that detects increased velocity through the proximal renal artery (this is only here for exposure, you are not expected to interpret any part of this image). (b) MRA demonstrating right renal artery stenosis, indicated by the absence of signal. It is merely coincidental that both patients had right renal artery lesions. (c) Representative sectioned adrenal gland demonstrating moderate diffuse hyperplasia that is nodular in some locations.

Chronic secondary aldosteronism (acute forms are not going to be discussed) come down to renovascular hypertension and fibromuscular dysplasia. Both conditions cause **renovascular hypertension**. An increase in resistance of one or both renal arteries, leading to poor perfusion of the glomeruli despite a normal blood pressure, results in excess renin production and, therefore, excess angiotensin-2. The patient has hypertension secondary to a vascular lesion of the renal arteries (reno-vascular hypertension). **Renal artery stenosis** (old white men with atherosclerosis elsewhere) and **fibromuscular dysplasia** (young women with no disease anywhere else) cause increased resistance in the renal artery. This reduces flow to the glomeruli, which perceive the reduced flow because of reduced renal blood flow.

If the problem is renovascular hypertension, the substrate will dictate what steps are taken. A young woman with fibromuscular dysplasia **should be stented**, restoring blood flow to her kidneys. A very old man with atherosclerotic disease and blocked vessels in other places (stroke, coronary artery disease, limb ischemia) **should not be stented** but rather treated with anti-RAAS medications (ACE/ARB for Ang-2, aldosterone antagonist for aldosterone). In patients with end-stage renal disease, aggressive blood pressure control is indicated because the renal effects are pointless.

Hypoaldosteronism

We saw this with adrenocortical insufficiency. The absence of aldosterone results in the wasting of sodium, and with it circulating volume, into the urine. This presents with hypotension, hyperkalemia, and death.

Fludrocortisone is given to patients who have hyperkalemia following adrenalectomy for a unilateral aldosterone-producing adenoma. With excess aldosterone and deficient renin, the contralateral, normal adrenal gland may not have received the trophic signals it needs to be ready to function right away. Most patients merely taper as the other adrenal gland warms back up.